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Research Submission

Wear-Off of OnabotulinumtoxinA Effect Over the Treatment Interval in Chronic Migraine: A Retrospective Chart Review With Analysis of Headache Diaries

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Objective.—To quantify wear-off of the response to OnabotulinumtoxinA (OnabotA) treatment over the treatment cycle in chronic migraine at group and individual level.

Background.—OnabotA administered quarterly is an effective treatment for chronic migraine. However, some patients report that headache recurs before the scheduled follow-up injection.

Methods.—In this retrospective chart review performed in 6 university outpatient centers or private practices specialized in headache treatment, 112 patients with a ≥30% response to OnabotA who completed headache diaries over 13 weeks after OnabotA treatment were included (age [mean ± SD] 45 ± 12 years, 82% female, headache days/month at baseline 24 ± 6).

Results.—Compared to weeks 5 to 8 after injection, headache days/week increased significantly in weeks 12 (+0.52 ± 1.96, 95% CI [0.15, 0.88], $P < .009$) and 13 (+1.15 ± 1.95, CI[0.79, 1.52], $P < .001$), demonstrating significant wear-off of the OnabotA effect. Similarly, acute medication days/week significantly increased in weeks 12 (0.38±1.67, CI [0.06, 0.69], $P \leq .027$) and 13 (+0.83 ± 1.76, CI [0.49, 1.16], $P < .001$). At an individual level, 57 patients (51%) showed ≥30% wear-off by weeks 12 and 13, and 28 patients (25%) showed ≥30% wear-off already by weeks 10 and 11. Age, gender, OnabotA dose or cycle number, or headache center did not predict individual wear-off.

Conclusions.—These data show that in clinical practice, on average the response of chronic migraine patients to OnabotA injection shows a clinically significant wear-off from week 12 after treatment. About 25% of the patients experience wear-off even by weeks 10 and 11. It must be noted that wear-off detected in a real-world study on OnabotA responders can be due to wear-off of a pharmacological OnabotA effect or a placebo effect, or to regression to the mean effects. This wear-off phenomenon may negatively affect quality of life of chronic migraine patients under OnabotA treatment. The best way to counteract wear-off remains to be determined.

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Abbreviations: ANOVA analysis of variance, ICHD-3 International Classification of Headache Disorders, 3rd edition, OnabotA OnabotulinumtoxinA, PREEMPT Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy, U.S. United States

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INTRODUCTION

Chronic migraine is a highly disabling headache disorder, often difficult to treat, and affecting 1.4-2.2% of the population.[1-4] In 2010, 2 large phase 3 studies (the Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies) demonstrated the efficacy and safety of OnabotulinumtoxinA (OnabotA) in the treatment of chronic migraine.[5,6] Since then, OnabotA treatment has been widely used for treatment of refractory chronic migraine, and numerous real-world studies have corroborated the PREEMPT study results.[7-10] In a pooled analysis of the PREEMPT studies, 49% of patients experienced a ≥50% reduction of headache days per month (a ≥50% response) and 71% experienced a ≥30% response in the first injection cycle.[11] Because of the large impact of chronic migraine on quality of life (QoL), European guidelines consider a ≥30% response as sufficient to continue OnabotA treatment.[12]

In clinical practice, some patients that respond to OnabotA therapy complain that the response wears off before the repeat injection is due. A 12-week interval between injections is recommended. However, for practical reasons, repeat injections are often scheduled at 3 months or later. Real-life data from large studies shows that, at least in Europe, the treatment interval is ≥13 weeks for most patients.[13,14] Maintaining a clinically significant response over the entire treatment cycle is important for achieving a stable long-term improvement in QoL in chronic migraine patients. Several studies have suggested important wear-off of the OnabotA effect over the treatment cycle in chronic migraine,[15-17] but a systematic investigation of the time course using headache diaries is currently lacking.

Our hypothesis was that a statistically and clinically significant wear-off of the OnabotA effect with respect to headache days per week would occur at week 13 after injection, maybe even earlier during the treatment cycle. To this end, we retrospectively analyzed headache diaries from chronic migraine patients with a ≥30% response to OnabotA. In addition to evaluating wear-off at the group level, individual wear-off was

Conflict of Interest: All authors (except IF and RO) have participated as trainees or mentors in an Allergan international education program with several meetings (the "Rising Stars" program), which provided a setting where headache investigators from around the world could meet and work on their study ideas. The present study was conceived within this setting. Beyond that, the project did not receive funding from Allergan. RR has received travel grants and honoraria for talks and/or advisory boards from Allergan, Lilly, Teva, Hormosan, and Novartis. BA has received travel grants or honoraria from Allergan, Teva, and Novartis. AGD has received honoraria as a speaker and travel grants from Allergan and honoraria as a speaker from Novartis. IF declares no conflict of interest. NL reports speaking fees from Allergan, Novartis, and Teva and travel grants from Allergan. RO received travel grants from Novartis and Teva. PP-R has received honoraria as a consultant and speaker for Allergan, Almirall, Biohaven, Chiesi, Eli Lilly, Medscape, Neurodiem, Novartis, and Teva. Her research group has received research grants from Allergan, AGAUR, la Caixa foundation, Migraine Research Foundation, Instituto Investigación Carlos III, MICINN, Novartis, PERIS; and has received funding for clinical trials from Alder, Electrocore, Eli Lilly, Novartis, and Teva. She is a trustee member of the board of the International Headache Society and a member of the Council of the European Headache Federation. She is in the editorial board of Revista de Neurologia. She is an associate editor for Cephalalgia, Frontiers of Neurology and Journal of Headache and Pain. She is a member of the Clinical Trials Guidelines Committee of the International Headache Society. She has edited the Guidelines for the Diagnosis and Treatment of Headache of the Spanish Neurological Society. She is the founder of www.midolordecabeza.org. PPR does not own stocks from any pharmaceutical company. SS received fees as speaker or for participation to advisory boards from Abbott, Allergan, Eli-Lilly, Medscape, Novartis, Teva. MTF reports speaking fees from Allergan, Novartis, Lilly, and Chiesi and travel grants from Allegan and Novartis, outside the submitted work. CS has received travel grants and honoraria from Allergan and served on advisory boards and received honoraria from Novartis and Teva.

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also analyzed, and the relation of wear-off to demographic factors and headache and treatment characteristics was investigated.

METHODS

Patients.—The study was conducted as a retrospective chart review performed in 6 university outpatient centers or private practices specialized in headache treatment around the world (Barcelona/Spain L'Aquila/Italy, Melbourne/Australia, Moscow/Russia, Munich/Germany, and Wroclaw/Poland). Research was conducted according to the declaration of Helsinki and ethics approval for retrospective data analysis was obtained from the local ethics committees where necessary (LMU Munich: 19-460, University of L'Aquila: 0203392/16, Vall d'Hebron: PR(AG)05/2017, Silesian Medical Board: 4/BNBO/2019, Austin Health HREC/54628/Austin-2019). As this was a retrospective, fully anonymized data collection of data obtained during standard patient care, written informed consent was waived by the ethics committees. Data collection by review of the charts of the past 2 years was performed between 6/2019 and 12/2019 at the different centers. Therefore, included data stemmed from OnabotA treatments performed between 6/2017 and 9/2019 (and the respective 13 week follow-up period). Inclusion criteria were as follows: (1) adult (≥18 years old); (2) diagnosis of chronic migraine according to the third edition of the International Classification of Headache Disorders (ICHD-3) criteria;[3] (3) history of inadequate response to oral prophylactic migraine treatment; (4) treated with their first, second, third, or fourth OnabotA injection according to the PREEMPT protocol (155 to 195 units);[18] (5) being a responder to OnabotA in the analyzed treatment cycle (defined as improvement in headache days per month ≥30% compared to the headache frequency before OnabotA); (6) having an interval to the subsequent OnabotA injection of ≥13 weeks; (7) having a completed headache diary providing daily information on headache intensity (none, mild, moderate, severe) and intake of acute headache medication (yes/no) for 13 weeks after the OnabotA injection; and (8) no new preventive migraine medication or change of dose during the 13 week observation period. Only one treatment cycle per patient was analyzed. Where more than one treatment cycle fulfilled the above criteria, the first available cycle was included. No missing data were allowed regarding the daily headache intensity. There were 4 patients without information on daily medication intake. Headache diaries are the gold standard for assessing headache frequency and other daily headache-related parameters. Short paper-and-pencil or electronic headache diaries as used in the present study have good reliability and validity.[19]

Demographic data and headache and treatment characteristics were extracted from the charts (Table 1).

Endpoints, Power Analysis, and Statistics.—SPSS Statistics version 25 (IBM, Armonk, NY, USA) was

Table 1.—Characteristics of the Study Population (n = 112)

Factor	
Gender	92 females (82%)
Age [years]	45 ± 12 (21-78)
Headache duration [years]	25 ± 12 (2-60)
Headache days per month before starting OnabotA treatment	24 ± 6 (15-31)
Concomitant oral migraine prophylaxis†	72 (64%)
Headache center	Barcelona, Spain: 11 (10%) L'Aquila, Italy: 16 (14%) Melbourne, Australia: 35 (31%) Moscow, Russia: 9 (8%) Munich, Germany: 15 (14%) Wroclaw, Poland: 26 (23%)
OnabotA dose group	155 units: 56 (50%) 160-190 units: 27 (24%) 195 units: 29 (26%)
OnabotA cycle	Cycle 1: 62 (55%) Cycle 2: 28 (25%) Cycle 3: 9 (8%) Cycle 4: 13 (12%)
Response to OnabotA treatment‡	63% (30-100%)

Data are given as mean ± standard deviation and range or as numbers and percentages, as adequate.

†Drugs used for oral migraine prophylaxis were (multiple mentions possible): topiramate n = 21, amitriptyline 22, other antidepressants 10, β-blocker 17, angiotensin II inhibitor 6, valproate 3, gabapentine/pregabaline 3, magnesium 3, riboflavin 2, pizotifen 2, melatonin 1, quetiapine 1, verapamil 1, cyproheptadine 1, zonisamide 1.

‡OnabotA response was quantified as percent reduction in headache days in weeks 5-8 of the current OnabotA cycle compared to the headache frequency before starting OnabotA treatment.

used. A P value <.05 was considered statistically significant and 2-tailed testing was used throughout. Means and SD, numbers and proportions (in %), or medians and interquartile ranges are reported as appropriate unless indicated otherwise. About 95% confidence intervals (CI) are reported for pairwise comparisons. Headache days *per week* (not month) were used to allow analysis of wear-off after OnabotA injection on a weekly basis. Week 1 after OnabotA injection was defined to include days 1-7 after injection, week 2 days 8-14, and so on.

This is the primary analysis of these data. Analysis of the primary and secondary endpoints was performed according to the preestablished study protocol, which also included the power analysis as detailed below. Additional (not preplanned) analyses were performed as indicated below.

Our hypothesis was that wear-off of OnabotA effect would occur in week 13 after injection or even earlier. The full effect of OnabotA was presumed to occur in weeks 5-8. Therefore, our preplanned primary endpoint was the comparison of the number of headache days per week in week 13 with the average of weeks 5-8, using Wilcoxon's test. If this was significant, analysis was repeated for week 12 and so on, until encountering a nonsignificant result. This corresponds to a fixed sequence approach to control for multiple comparisons, as also used in previous studies on OnabotA.[5] The same procedure was followed for the preplanned secondary endpoints: (1) number of moderate to severe headache days per week and (2) number of acute headache medication days per week.

A power analysis for the primary endpoint was performed before starting the study. In the pooled PREEMPT analysis,[18] patients had 19.3 ± 3.7 headache days/28 days before OnabotA treatment. After 2 injection cycles, headache days were reduced by 8.4 days/28 days. To detect wear-off of +2.1 headache days/28 days, that is, +0.525 headache days per week (corresponding to 25% of the total OnabotA effect), assuming an increased standard deviation because of the shorter observation period of 1 week (6.0), 109 patients are needed to detect this effect at $P < .05$ and a power of 0.95 (calculation performed with G*Power, http://www.gpower.hhu.de/).

An additional (not preplanned) analysis of wear-off at an individual level was performed. Individual wear-off was detected if the number of headache days per week in weeks 12 and 13 (combined) was ≥30% higher than in weeks 5-8. Early wear-off was detected if the number of headache days per week in weeks 10 and 11 (combined) *and* in weeks 12 and 13 (combined) was ≥30% higher than in weeks 5-8. Two week intervals were used for the individual analysis to increase robustness of the results. Correspondingly, *percentage wear-off* at an individual level was quantified as ((average number of headache days per week in weeks 12 and 13)-(average number of headache days per week in weeks 5-8))/(average number of headache days per week in weeks 5-8) × 100. In addition, *difference wear-off* was quantified at an individual level as ((average number of headache days per week in weeks 12 and 13)-(average number of headache days per week in weeks 5-8)).

Finally, the relation of demographic, headache, and treatment parameters to individual wear-off was tested using Kruskal-Wallis test or Spearman's correlation as appropriate.

RESULTS

A total of 112 chronic migraine patients were included in the analysis. Demographic data and characteristics of headache and treatment are listed in Table 1. Throughout the Results section, "significant" designates "statistically significant."

Wear-Off at Group Level.—This analysis is based on average numbers of headache days, moderate to severe headache days and acute medication days *per week*. The average number of headache days per week showed a significant wear-off of the response to OnabotA injection in weeks 12 and 13 after treatment (Fig. 1A). Compared with the average of weeks 5 to 8 after injection (2.23 ± 1.21 days per week, considered to reflect the period of full OnabotA effect), headache days were significantly increased in week 13 (by +1.15 ± 1.95, 95% CI [0.79, 1.52], $Z = -5.4$, $P < .001$) and in week 12 (+0.52 ± 1.96, CI [0.15, 0.88], $Z = -2.6$, $P = .009$) but not in week 11 (−0.11 ± 1.67, CI [−0.42, 0.21], $Z = -1.3$, $P = .201$). For moderate-severe headache days (Fig. 1B), a significant increase compared to the average of weeks

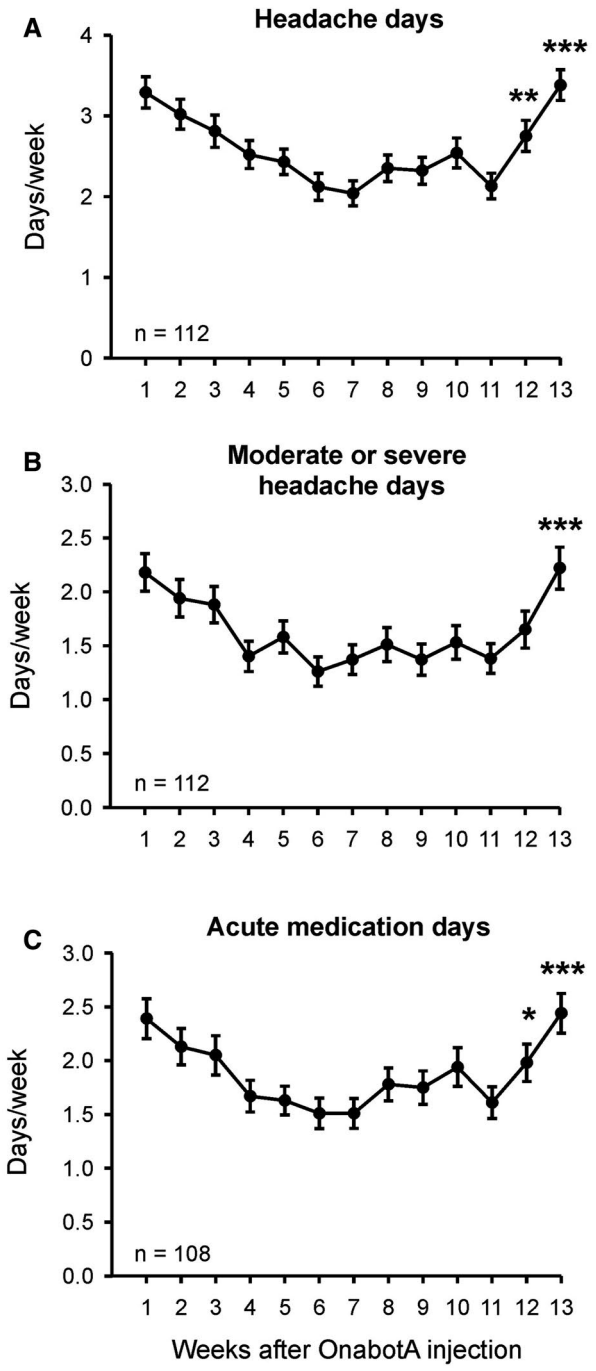

Fig. 1.—Time course of headache parameters over 13 weeks after OnabotA treatment. (A) headache days per week, (B) moderate or severe headache days per week, (C) acute medication days per week. *$P < .05$; **, $P < .01$; ***$P < .001$ for the comparison of the respective week with the average of weeks 5-8 using Wilcoxon's test. Values are mean ± standard error of the mean (SEM). We used SEM instead of standard deviation (SD) for better visualization of the time course of headache parameters over the treatment cycle. Exact means and SD can be found in the Supporting Information.

5-8 (1.43 ± 1.19 days per week) was detected in week 13 (+0.79 ± 1.80, CI [0.46, 1.13], $Z = -4.3$, $P < .001$) but not in week 12 (+0.22 ± 1.66, CI [−0.09, 0.53], $Z = -0.8$, $P = .436$). Regarding days with use of acute headache medication (Fig. 1C), these were significantly higher in weeks 13 (+0.83 ± 1.76, CI [0.49, 1.16], $Z = -4.4$, $P < .001$) and 12 (+0.38 ± 1.67, CI [0.06, 0.69], $Z = -2.2$, $P = .027$) but not in week 11 (+0.005 ± 1.48, CI [−0.29, 0.27], $Z = -0.6$, $P = .537$) after injection, compared to the average of weeks 5 to 8 (1.61 ± 1.04 days per week).

Individual Wear-Off and Factors Related to Individual Wear-Off.—At the individual level, 57 patients (51% of the total group) showed ≥30% wear-off of the response to OnabotA injection, quantified by headache days per week in weeks 12/13 after injection (compared to weeks 5-8). Early wear-off was detected in 28 patients (25% of the total group), who had ≥30% wear-off both in weeks 10/11 and in weeks 12/13.

There was a 33.3% median individual wear-off in weeks 12/13 (interquartile range IQR: −7% to +100%). There was no influence of gender, age, headache duration, headache days per month before OnabotA treatment, OnabotA dose group, OnabotA cycle number, the treating headache center, or concomitant use of oral migraine prophylaxis on individual percentage wear-off (Table 2).

As the individual percentage wear-off scores tend to inflate in patients with a very good treatment response (ie, few headache days in weeks 5-8), leading to a considerably skewed distribution of the variable, we used the absolute difference in headache days per week between weeks 12/13 and weeks 5-8 as an alternative measure of wear-off. This measure was much less skewed, with a median of +0.75 (IQR −0.29 to 1.50) and a mean ± SD of +0.83 ± 1.64 headache days per week (range −2.00 to +6.75). Similar to the results reported above, none of the factors was significantly related to the individual difference wear-off (not shown).

DISCUSSION

The main result of the present study is that in clinical practice, a both statistically and clinically significant wear-off of the preventive effect of OnabotA injections in chronic migraine occurs starting in week

Table 2.—Factors Related to Individual Wear-Off (n = 112)

Factor	Median (IQR) of the Individual Percentage Wear-Off	Statistics
Gender	F: 31% (0-100) M: 37% (−18-79)	H = 0.1, *P* = .752
Age		rho = 0.05, *P* = .571
Headache duration [years]		rho = −0.04, *P* = .683
Headache days per month before starting OnabotA treatment		rho = −0.02, *P* = .869
Concomitant oral migraine prophylaxis	No: 33% (−16-100) Yes: 33% (0-100)	H < 0.01, *P* = .995
Headache center (1-6)		H = 6.1, *P* = .294
OnabotA dose group (1-3)	155 units: 40% (0-100) 160-190 units: 33% (0-133) 195 units: 14% (−22-80)	H = 1.8, *P* = .415
OnabotA cycle (1-4)	Cycle 1: 33% (−3-100) Cycle 2: 23% (−20-291) Cycle 3: 50% (10-122) Cycle 4: 27% (−7-71)	H = 0.9, *P* = .823

Results of Kruskal-Wallis ANOVA (H values) with individual wear-off (in percent) as independent variable or Spearman's correlations (rho coefficients) with individual wear-off (in percent) are shown.
IQR = interquartile range.

12 at the group level. At an individual level, 51% of the patients had wear-off at weeks 12 and 13, and 25% of patients had wear-off as early as weeks 10 and 11.

Wear-Off of the Response to OnabotA Treatment in Chronic Migraine.—The present study extends previous data on wear-off of OnabotA effect[15-17] by using weekly analysis of headache diaries. This characterizes more clearly the time course of OnabotA effect and the time point of onset of significant wear-off at group level (week 12). In addition, it corroborates the presence of wear-off by showing that acute headache medication use increased starting from week 12 and moderate-to-severe headache days increased starting from week 13.

Three previous studies have also suggested a wear-off effect of OnabotA effect during the treatment cycle in chronic migraine. A study from Spain analyzed 193 patients during their first treatment cycle, of which 70% had a 50% response in weeks 5-8. Of these, two-thirds maintained a 50% response until week 12 (full-length responders), while one-third no longer had a ≥50% reduction of headache days when weeks 7-10 or 9-12 were considered (wearing-off responders). The number of headache days or the precise timing of wear-off were not reported.[15] The second study included 143 patients from the United States (U.S.). Both response to OnabotA and wear-off were identified from the physician's notes. Headache diaries were not analyzed. Two-thirds of patients were reported to show wear-off between weeks 6 and 12, especially during the first cycle.[16] Another study from the U.S. included 98 patients with multiple (≥2) treatment cycles. The response to OnabotA was not quantified. Wear-off was identified from spontaneous patient reports of reduction of effect in the last 4 weeks of the treatment cycle (maximum 13 weeks) as documented in the medical notes. Wear-off was detected in 19% of treatment cycles. About 44% of the patients reported wear-off at least once, and 19% more than once.[17]

Duration of Action on OnabotA in Other Indications and Animal Models.—In prevention of chronic migraine, OnabotA is thought to act on primary afferent C-fibers.[20] To the best of our knowledge, the duration of action of OnabotA on C-fibers has not been investigated. It may therefore be helpful to consider the duration of action in other OnabotA targets. Exocytotic function of mouse motor neurons is lost after botulinum neurotoxin A injection, but partially functional dendritic sprouts appear at 28 days and normal function of the original nerve terminal is recovered after 91 days.[21,22] Howev-

er, the time course in humans and mice may differ. The median duration of action in the human frontalis muscle is 77-87 days, that is, approximately 12 weeks.[23] In the treatment of motor disorders the duration of action is presumed to be around 3 months. In axillary hyperhidrosis, the duration of action of OnabotA is >6 months.[24] The median time to request re-treatment with OnabotA in neurogenic detrusor overactivity was 42 weeks (10 months).[25] In summary, results in different indications are very variable and cannot be directly extrapolated to OnabotA treatment of chronic migraine.

Prediction of OnabotA Wear-Off.—It would be useful to be able to predict wear-off in individual chronic migraine patients before OnabotA treatment. However, in the present study, neither gender, age, headache duration, headache days per month before OnabotA treatment, OnabotA dose, treatment cycle, nor the concomitant use of an oral migraine preventive medication predicted individual wear-off. It must also be considered that only one treatment cycle was analyzed for each patient, so that conclusions about continued treatment cannot be made. Similarly, neither the Spanish nor the first U.S. study identified predictors of wear-off (age, gender, presence of medication overuse, migraine duration, acute medication frequency, and psychiatric comorbidity were tested).[15,16] There was a tendency for patients with more headache days at baseline to experience more wear-off in the Spanish study.[15] The second U.S. study identified motion sickness and history of infectious meningitis as risk factors, though they did not correct multiple comparisons.[17]

Possible Strategies to Counteract OnabotA Wear-Off.—The present data demonstrate that, at least within the first 4 treatment cycles, 13 weeks intervals are not sufficient to maintain a continuing response to OnabotA treatment in many patients, and that an important number of patients show wear-off even earlier, starting at 10 weeks. It must also be considered that patients who experience wear-off may have a prolonged period of high headache frequencies around the date of their repeat injection, as the maximum effect of OnabotA treatment in chronic migraine does not manifest immediately after the injection (see present data and Dodick et al[26]).

Further research is needed to find strategies to counteract OnabotA wear-off. A first step would be to stick to 12-week treatment intervals at least during the first few cycles to keep the period of potential wear-off as short as possible while staying within the license. Next, it will be necessary to determine if wear-off is a self-limiting problem occurring preferentially during the first few treatment cycles. However, previous research on self-reported wear-off over ≥2 cycles suggested that ~20% of the patients experience repetitive wear-off.[17] On the contrary, it has been reported that injections may successfully be delayed without exacerbation of headache in some patients, especially after the first year of treatment.[27,28] Reducing injection intervals to less than 12 weeks would be a possible strategy to counteract wear-off in selected patients with repeated wear-off. However, this must be weighed against the possibility to promote formation of neutralizing antibodies in long-term treatment.[29,30] Some authors have suggested that increasing the dose might prolong the OnabotA effect,[15,16] but systematic data are missing, and increased doses may also bear the risk of antibody formation. Our study did not reveal an association between OnabotA dose used (within the 155 to 195 unit range) and wear-off. A previous study found no difference in median dose in patients with one vs multiple cycles with self-reported wear-off.[17] As the reasons for individual choice of dose are not known, these data must be interpreted with caution. Moderately increasing the dose up to 195 units, as provided for in the PREEMPT protocol, could be attempted to handle repetitive wear-off until more data are available.

Strengths and Limitations.—The most important strength of the present study is that it used quantitative headache diary data to precisely assess numbers of headache days on a weekly basis, which identified the onset of OnabotA wear-off at group level. In addition to headache days, wear-off was corroborated by data on acute headache medication use per week. A further strength is the data collection at several headache centers around the world, reducing bias.

It must be considered that the present study describes wear-off after OnabotA treatment as seen in real-world clinical practice, not under controlled conditions. To answer the clinically relevant question *if* and *at what time point* during the treatment cycle chronic migraine patients who initially improved after OnabotA treatment show wear-off of the initial effect, we included only patients with an at least ≥30%

improvement of headache days per in week 5-8 after treatment (presumed to reflect the maximum OnabotA effect). It must be noted that in a real-world, uncontrolled study, improvement after OnabotA injection can be due to the pharmacological OnabotA effect (which exists as demonstrated by the PREEMPT studies[5,6]), and also to a placebo effect, or to chance (natural fluctuations in migraine frequency). Therefore, the wear-off observed under the present conditions can be due to wear-off of the specific effect of OnabotA, due to wear-off of a placebo response or due to regression to the mean that follows a reduction of headache frequency that occurred by chance. In addition, wear-off as detected in the present study might be influenced by a nocebo effect, as patients may expect wear-off to occur, for example, because they have been told that the effect normally lasts about 12 weeks. The relative proportions of these mechanisms cannot be estimated in a real-world study. Nonetheless, the results represent wear-off of response to OnabotA treatment as encountered in clinical practice.

It is a further limitation that the present data are limited to patients receiving their first to fourth OnabotA treatment for chronic migraine and evaluated only one treatment cycle. In fact, our study was focused on detecting wear-off early during OnabotA treatment, and most of our data stemmed from cycles 1 and 2. Therefore, our results cannot be generalized to later cycles. Longitudinal studies would be very useful to investigate if the wear-off phenomenon is self-limiting (ie, disappears with continued treatment) and if it affects the same patients in subsequent cycles.

As the real duration of effect of OnabotA in chronic migraine is not known, we decided to call the reduction of effect wear-off, irrespective of whether it occurred within the recommended dosing interval of 12 weeks (early wear-off) or after that time (which might be interpreted as expected reduction of effect).

CONCLUSION

The present study used data from headache diaries to show statistically and clinically significant wear-off of the headache preventive effect of OnabotA treatment in chronic migraine at the group level starting in week 12 after treatment. At an individual level, wear-off as determined in a single treatment cycle was present as early as in weeks 10 and 11 for 25% of the patients. No predictors of OnabotA wear-off could be identified. It must be noted that wear-off detected in a real-world study on OnabotA responders includes wear-off of pharmacological OnabotA effects, of placebo effects, or regression to the mean effects.

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